Cancer Cytopathology 2018 Young Investigator Challenge: Subtyping Salivary Gland Neoplasm of Uncertain Malignant Potential Based on Cell Type Demonstrates Differential Risk of Malignancy

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Running title: Subtyping SUMP

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AUTHOR CONTRIBUTIONS

Jen-Fan Hang: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, visualization, writing - original draft, and writing - review and editing. **Fatimah Alruwaii:** Data curation and investigation. **Bao-Rung Zeng:** Data curation and investigation. **Chiung-Ru Lai:** Resources, supervision, visualization, and writing–review and editing. **Howard H. Wu:** Conceptualization, data curation, investigation, resources, supervision, visualization, and writing–review and editing.

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Condensed Abstract

A 12-year, bi-institutional, retrospective review showed that *Salivary Gland Neoplasm of Uncertain Malignant Potential* (SUMP) comprised 5.9% (92/1560) of all salivary gland aspirates, with an overall risk of malignancy (ROM) of 40.7% (24/59). Subtyping SUMP as oncocytic/squamoid, basaloid, or myoepithelial subtypes demonstrated differential ROM of 61.1% (11/18), 40.0% (10/25), and 18.8% (3/16), respectively (P=0.0476).

Abstract

Background

The newly unveiled Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) has proposed *Salivary Gland Neoplasm of Uncertain Malignant Potential* (SUMP) as an indeterminate category. The category is reserved for fine needle aspiration (FNA) cases that are diagnostic of a salivary gland neoplasm but cannot be further designated to a specific tumor type. This study aimed to evaluate the clinical utility of subtyping SUMP cases based on different cell type.

Methods

A retrospective search of cytology databases at two institutions for salivary gland FNA from 2006-2017 was conducted. The cytologic diagnosis of each case was reclassified according to the MSRSGC. Histologic follow-up was retrieved for correlation. Cases reclassified as SUMP that had a follow-up pathologic diagnosis were subject to cytology review and subtyping into oncocytic/squamoid, basaloid, or myoepithelial subtypes based on cytomorphology. The risk of malignancy (ROM) for each subtype was analyzed.

Results

There were 92 SUMP cases, which comprised 5.9% of 1560 consecutive salivary gland FNA within the 12-year period. Histologic follow-up was available in 59 patients. After cytology review, there were 18 (30.5%) cases of oncocytic/squamoid subtype, 25 (42.4%) of basaloid subtype, and 16 (27.1%) of myoepithelial subtype. Pathologic correlation revealed ROM of 61.1% (11/18) for oncocytic/squamoid subtype, 40.0% (10/25) for basaloid subtype, and 18.8% (3/16) for myoepithelial subtype. The differences in ROM among the three subtypes were statistically significant (P=0.0476).

Conclusion

Subtyping SUMP category based on cell type demonstrated differential ROM for better clinical stratification. Future prospective studies are mandatory to confirm this finding.

Keywords: The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC), salivary gland neoplasm of uncertain malignant potential (SUMP), fine needle aspiration (FNA), salivary gland, cytology

Introduction

Salivary gland fine needle aspiration (FNA) is among the most challenging fields in diagnostic cytopathology. The wide morphologic spectrum of salivary gland cytology reflects the complexity of salivary gland pathology. There are various types of tumors in the salivary glands. The newly updated 2017 World Health Organization classification has listed more than 30 types of benign and malignant salivary gland epithelial tumors, in addition to other tumors of hematopoietic or soft tissue origins.[1] The morphologic heterogeneity may occur in a single tumor type due to tumor differentiation, metaplasia, tissue change or reaction. For example, it is not uncommon to see squamous metaplasia or cystic change in a pleomorphic adenoma, causing diagnostic confusions.[2-5] Moreover, even a single cell type can present with diverse cytomorphology. For instance, myoepithelial cells can be spindle-shaped, epithelioid, plasmacytoid, or even clear.[6] Besides, non-neoplastic tumor-like salivary gland lesions as well as other primary tumors occur in lymph node, soft tissue, or skin adjacent to the salivary glands can clinically mimic a salivary gland tumor for FNA evaluation.[7] Therefore, although a specific cytologic diagnosis is not difficult in many common salivary gland tumors, rare tumor types, selective sampling, or misleading anatomic locations of FNA can sometimes lead to major misdiagnosis.[8-10]

The recently unveiled Milan System for Reporting Salivary Gland

Cytopathology (MSRSGC) aims to provide an internationally recognized, uniform reporting system with standardized terminology to replace the conventional, descriptive interpretation for salivary gland FNA.[11] The 7-tiered classification includes non-diagnostic (I), non-neoplastic (II), atypia of undetermined significance (AUS, III), benign neoplasm (IVa), salivary gland neoplasm of uncertain malignant potential (SUMP, IVb), suspicious for malignancy (SM, V), and malignant (VI).[12] The SUMP category is reserved for a small but heterogeneous group of cases with cytomorphologic features diagnostic of a neoplasm but indefinitive for a specific tumor type to further distinguish between benign or malignant. In our experience, a majority of the most formidable salivary gland FNA cases will now be classified under this indeterminate diagnostic category. However, the various histologic follow-up in this group may cause uncertainty in clinical management. The objectives of this current study were to better characterize SUMP cases by subtyping them based on different cell type and to evaluate the clinical utility of this practice.

Materials and Methods

Case Selection

The study was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (IRB No.: 2018-07-009AC) and Indiana University (IRB

No.: 1802116631). A retrospective search for cytopathology archives at Taipei Veterans General Hospital and Indiana University for salivary gland FNA cases during a 12-year period (from January 1st, 2006 to December 31st, 2017) was performed. The procedure of salivary gland FNA was similar between the two institutions. Briefly, aspirates were performed by surgeons or radiologists with or without ultrasonographic guidance using 23- to 25- gauge needles. Two to four passes were obtained from each lesion. The smears were prepared with conventional methods. The air-dried slides were stained for Romanowsky-type stains (either Liu or Diff-Quik) and the alcohol-fixed slides were stained for Papanicolaou stain. Based on the cytology reports and slide review when information from the report was insufficient, all the cases were reclassified using the recently proposed MSRSGC terminology and criteria.[12] Clinical information and final pathologic diagnosis were recorded from the medical chart.

Slide Review and Subtyping SUMP Cases

For cases reclassified as SUMP, all available cytologic slides were retrieved for review and subtyping based on cell morphology. The oncocytic/squamoid subtype is characterized by epithelial cells with moderate to abundant amounts of cytoplasm. The cytoplasm is either granular as it is in oncocytes or dense as in squamoid cells.

The nucleus is centrally located and often with a small but distinct nucleolus. The distinction between oncocytic and squamoid cells is sometimes unclear; therefore, this subtype includes both conditions. Rare cases with foamy or vacuolated cytoplasm are also allowed. The differential diagnosis includes Warthin's tumor, oncocytoma/oncocytosis, mucoepidermoid carcinoma, and rarely acinic cell carcinoma or secretory carcinoma (Figure 1 and 2). The basaloid subtype is characterized by basaloid tumor cells with scant cytoplasm. This subtype is often associated with sharply marginated extracellular matrix of various morphologic features. The main differential diagnosis is basal cell neoplasm versus adenoid cystic carcinoma (Figure 3). The myoepithelial subtype applies to two circumstances. Firstly, it can be used for cases showing classic features of benign pleomorphic adenoma, while focal cellular atypia is conspicuous (Figure 4A-B). In this situation, the differential diagnosis is benign pleomorphic adenoma with focal atypia versus non-invasive or invasive carcinoma ex pleomorphic adenoma. For the second situation, the cases are composed of predominantly myoepithelial cells but chondromyxoid stroma is usually not evident (Figure 4C-D). The main differential diagnosis is cellular pleomorphic adenoma versus myoepithelioma or myoepithelial carcinoma.

Statistical Analyses

Data were summarized using descriptive statistics. Mean and range were used for continuous variables, whereas count and frequency were used for categorical variables. Fisher's exact tests were performed to compare proportions of categorical variables. ANOVA tests were performed to test differences among means of multiple groups. Two-sided P values < 0.05 were considered to be statistically significant. Statistical analyses were performed with R software (version 3.5.0; R Foundation, Vienna, Austria).

Results

Reclassification of the Study Cohort

A total of 1560 salivary gland aspirates was identified (675 from Taipei Veterans General Hospital and 885 from Indiana University) in this 12-year period. The result of reclassification based on the MSRSGC diagnostic categories was followed: non-diagnostic in 293 (18.8%), non-neoplastic in 337 (21.6%), AUS in 60 (3.8%), benign neoplasm in 581 (37.2%), SUMP in 92 (5.9%), suspicious for malignancy in 19 (1.2%), and malignant in 178 (11.4%). Histology follow-up was available in 694 (44.5%) cases. The risk of malignancy (ROM) for each category was followed: 17.1% (12/70) for non-diagnostic, 10.0% (8/80) for non-neoplastic, 37.5% (15/40) for AUS,

2.9% (9/315) for benign neoplasm, 40.7% (24/59) for SUMP, 100% (15/15) for suspicious for malignancy, and 98.3% (113/115) for malignant. These were comparable to the MSRSGC estimated ROM. A summary of this reclassification is shown in Table 1.

Clinical Characteristics of SUMP and Subtypes

Among the 59 patients who had FNA diagnosis of SUMP and available Histologic follow-up, there were 23 men and 36 women with a mean age of 56.3 years (range, 17-91 years). Fifty-two nodules were from the parotid glands and 7 were from the submandibular glands. The mean nodule size was 2.2 cm (range, 0.7-9.4 cm). After slide review (J.-F.H. reviewed the slides from Taipei Veterans General Hospital and H.H.W. reviewed the slides from Indiana University), the 59 aspirates of SUMP were designated to subtypes based on cell type. There were 18 (30.5%) cases of oncocytic/squamoid subtype, 25 (42.4%) of basaloid subtype, and 16 (27.1%) of myoepithelial subtype. For the myoepithelial subtype, 12 cases showed cellular myoepithelial aspirates and 4 showed focal atypia. Ancillary testing was not applied in any of the cases. The clinical characteristics are summarized in Table 2. There were no significant differences noted with regard to clinical features among patients of different SUMP subtypes, except sex (P=0.0379) of which female was more prevalent

in myoepithelial subtype.

Pathologic Correlation and ROM for Different SUMP Subtypes

The follow-up pathologic diagnoses for each SUMP subtype are listed in Table 3. Overall, 96.6% (57/59) of FNA diagnosed as SUMP were neoplastic. For oncocytic/squamoid subtype, the most common pathology was mucoepidermoid carcinoma (38.9%, 7/18) and Warthin's tumor (16.7%, 3/18). Of note, the only two non-neoplastic lesions, one salivary duct cyst and one chronic sialoadenitis, were both classified as this subtype. For basaloid subtype, the most common pathology was basal cell adenoma (41.7%, 10/24), followed by pleomorphic adenoma (20.8%, 5/24) and adenoid cystic carcinoma (16.7%, 4/24). For myoepithelial subtype, the most common pathology was pleomorphic adenoma (64.7%, 11/17).

The ROM for each SUMP subtype is shown in Table 4. The ROM was the highest for oncocytic/squamoid subtype (61.1%, 11/18), followed by basaloid subtype (40.0%, 10/25) and myoepithelial subtype (18.8%, 3/16). The differences in ROM among all three subtypes were statistically significant (P=0.0476). For the comparison of ROM between two subtypes, the ROM of oncocytic/squamoid SUMP was substantially higher than the myoepithelial SUMP (P=0.0173), while oncocytic/squamoid versus basaloid (P=0.2231) and basaloid versus myoepithelial

(P=0.1874) were both statistically insignificant. Even though the ROM of myoepithelial subtype was the lowest among all SUMP, it was still significantly higher than the benign neoplasm category (18.8% vs. 2.9%, P=0.016)

Discussion

FNA cytology is widely utilized for the evaluation of salivary gland nodules. It shows high specificity in diagnosis of some common benign epithelial neoplasms, such as pleomorphic adenoma and Warthin's tumor,[13] as well as frankly malignant high-grade carcinomas.[14, 15] However, to distinguish between a benign and a bland-looking, low- to intermediate-grade malignant tumor can be challenging due to cytomorphologic overlap and diversity.[7-10] For that reason, the MSRSGC has proposed SUMP as an indeterminate diagnostic category.[12] This category is reserved for FNA cases that are diagnostic of a neoplasm but the possibility of a malignant neoplasm cannot be excluded. Previous literatures suggested various approaches on the cytologic evaluation of these indeterminate neoplastic lesions. Some illustrated a simple scheme by separating these into two groups as basaloid neoplasm and salivary gland neoplasm with predominant oncocytic cell,[16] while others developed a more sophisticated manner considering cell type (basaloid or oncocytoid), variation of nuclear size (pleomorphic or monomorphic), stroma (fibrillary, hyaline, or mixed),

background materials (cystic, mucinous, or other), and cytoplasmic features (granular/vacuolated).[17] The MSRSGC has recommended three subcategories for SUMP, namely cellular basaloid neoplasm, cellular oncocytic/oncocytoid neoplasm, and cellular neoplasm with clear cell features.[18] In this current study, we subtyped SUMP cases based on three different cell types to comprise most of the diagnostic scenarios for indeterminate salivary gland FNA cases according to our own experiences. The rationale was to focus on the differential diagnoses associated with the three most common benign salivary gland neoplasms, that is, Warthin's tumor, basal cell adenoma, and pleomorphic adenoma, by separating these cases into oncocytic/squamoid, basaloid, and myoepithelial subtypes, respectively. Afterward, we examined the histologic follow-up and analyzed the ROM for each subtype to evaluate the clinical utility of this practice.

The oncocytic/squamoid subtype is characterized by neoplastic epithelial cells with moderate to abundant amounts of granular or dense cytoplasm. The diagnosis of benign oncocytic tumors, such as Warthin's tumor or oncocytoma/oncocytosis, is usually not difficult. In occasional cases; however, the presence of atypical features like squamous metaplasia, mucinous metaplasia, or mucoid background materials, will raise concern of a low-grade mucoepidermoid carcinoma.[19] On the other hand, when a mucoepidermoid carcinoma shows oncocytoid change, cystic debris, or

prominent lymphocytic infiltrates, it may overlap with the cytomorphologic features of a benign Warthin's tumor.[20] The histologic follow-up for oncocytic/squamoid subtype in this study revealed seven mucoepidermoid carcinomas (Figure 1A and D), three Warthin's tumors (Figure 2A-B), and one oncocytoma (Figure 2C-D). These tumors comprised 61.1% (11/18) of the cases. Although cellular neoplasm with clear cell features is proposed by the MSRSGC as a SUMP subcategory, we find that there is wide cytomorphologic overlap with oncocytic/squamoid subtype cases. Clear cell features are generally an artefactual phenomenon in histology due to formalin-fixation. The corresponding cytomorphologic features represent granular, foamy, or vacuolated cytoplasm, other than clear. The differential diagnoses are seldom benign but rather restricted in some less common malignant tumors, such as acinic cell carcinoma,[21] secretory carcinoma,[22, 23] hyalinizing clear cell carcinoma,[24] clear cell myoepithelial carcinoma,[25] rare cellular changes of mucoepidermoid carcinoma,[26] or metastasis.[27] If a specific diagnosis cannot be ascertained, this group of tumors may be better classified as suspicious for malignancy. In the oncocytic/squamoid subtype of SUMP, we accepted rare cases showing abundant foamy or vacuolated cytoplasm as a spectrum of oncocytoid cells. There were one acinic cell carcinoma (Figure 1B and E) and one secretory carcinoma (Figure 1C and F) on histologic follow-up. Other pathology included a salivary duct carcinoma showing scant atypical cells with

apocrine features that mimicked oncocytes, a pilomatrixoma presenting as a parotid mass and showing scant atypical squamoid cells, a non-neoplastic cyst containing abundant mucoid background and scant epithelial cells simulating a mucoepidermoid carcinoma, and two lymphoepithelial lesions (one chronic sialoadenitis and one extranodal marginal zone B cell lymphoma) resembling Warthin's tumor. Overall, the ROM of oncocytic/squamoid subtype was the highest in this study (61.1%), suggesting that surgical management should be highly recommended.

The basaloid subtype represents cases showing epithelial tumor cells with scant cytoplasm. The cells are often associated with sharply marginated, hyaline-type, extracellular matrix, which is better demonstrated by Romanowsky-type stain. To differentiate benign versus malignant tumors with basaloid features is a diagnostic challenge and sometimes impossible due to overlapping cytomorphology.[16, 28-30] In addition, certain types of extracellular matrix is non-specific for the diagnosis and sometimes misleading. Hyaline globules surrounded by basaloid cells are a characteristic feature of adenoid cystic carcinoma. However, this feature has been noted in benign basal cell adenoma (Figure 3C-D), pleomorphic adenoma, and myoepithelioma, and that may lead to false positive diagnosis.[2, 3, 28-30] Hyaline globules have also been seen in other malignant tumors like epithelial-myoepithelial carcinoma and polymorphous adenocarcinoma of minor salivary glands.[31, 32]

Membranous-type hyaline matrix wrapping around basaloid cell clusters is a common feature for basal cell adenoma.[30] Although less described in the literature, this feature may also present in an adenoid cystic carcinoma with predominant tubular pattern (Figure 3A-B), causing false negative diagnosis. Therefore, SUMP category is recommended for basaloid neoplasms without unequivocal cytologic features of carcinoma to avoid diagnostic discrepancy. Definite diagnosis should not be based on types of extracellular matrix alone for these tumors. In this study, the histologic follow-up for basaloid subtype showed ten basal cell adenomas, six pleomorphic adenomas (including one carcinoma ex pleomorphic adenomas), four adenoid cystic carcinomas, and two epithelial-myoepithelial carcinomas. These tumors comprised 88% (22/25) of the cases. The overall ROM of the basaloid subtype was 40% falling between the other two subtypes.

The myoepithelial subtype is reserved for tumors of myoepithelial differentiation showing indeterminate atypical features. The first scenario for this subtype is when focal questionable atypia is present in cases showing otherwise characteristic features of pleomorphic adenoma. Pleomorphic adenoma is the most common benign salivary gland neoplasm. Nevertheless, carcinomas may occasionally arise from pleomorphic adenomas and behave aggressively. Selective FNA sampling of carcinoma ex pleomorphic adenoma may cause false negative diagnosis. In previous studies, only

29-50% of cases had pre-operative FNA diagnosis of malignancy. [33-36] On the other hand, various degree of cellular atypia is not uncommon in benign pleomorphic adenoma and may be overcalled as malignant.[2, 3, 8] In the current study, there was one carcinoma ex pleomorphic adenoma out of the four myoepithelial subtype cases of focal atypia on histologic follow-up. The other three were all benign pleomorphic adenoma (Figure 4A-B). The second scenario applies to cases composed of predominately myoepithelial cells. The myoepithelial cells are often plasmacytoid with diffuse mild to moderate atypia (Figure 4C-D). The extracellular stroma may be present but usually not chondromyxoid in texture. The main differential diagnosis included cellular pleomorphic adenoma, myoepithelioma, basal cell neoplasm, and myoepithelial carcinoma.[6, 29] In this study, the histologic follow-up for cellular myoepithelial aspirates revealed 11 pleomorphic adenomas, one basal cell adenoma, one myoepithelial carcinoma, and one adenoid cystic carcinoma. Overall, the ROM for the myoepithelial subtype of SUMP was the lowest; however, it was still significantly higher than the benign neoplasm category (18.8% vs. 2.9%, P=0.016).

The recent molecular advances reveal several type-specific genetic alterations in salivary gland tumors.[37] Ancillary testing such as immunocytochemistry, fluorescent in-situ hybridization, or polymerase chain reaction has emerged and been increasingly used in cytopathology.[32, 38, 39] Nonetheless, more studies are still required to validate

the performance of these tests on cytologic specimens. Given that complete surgical excision is the standard treatment for most symptomatic salivary gland tumors, FNA confirmation of a neoplastic lesion is sufficient for following clinical management. A type-specific diagnosis seldom changes the procedure. For a practical point of view, imaging evaluation of the tumor border may provide further information regarding the extent of surgery.[40]

In conclusions, SUMP is a robust diagnostic category that comprised 5.9% of the total salivary gland FNA cases in this 12-year retrospective review. Among them, 96.6% had confirmed neoplastic diagnoses upon follow-up. Subtyping SUMP cases demonstrated differential ROM for oncocytic/squamoid (61.1%), basaloid (40.0%), and myoepithelial subtypes (18.8%) (P=0.0476). This simple and practical approach facilitates clinical stratification. Future prospective studies are mandatory to confirm this finding.

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Figure Legends

Figure 1. Oncocytic/squamoid subtype with malignant follow-up. (A) Oncocytoid cells with moderate amounts of cytoplasm admixed with few lymphocytes (Liu stain, X400). Follow-up excision showed an intermediate-grade mucoepidermoid carcinoma with prominent lymphocytic cuffing (D, H&E, X100). (B) Cellular fragments consisted of oncocytoid cells with finely granular cytoplasm (Papanicolaou, X400). Follow-up excision showed an acinic cell carcinoma (E, H&E, X200). (C) Loosely cohesive cell fragments comprised oncocytoid cells with dense cytoplasm. Proteinaceous fluid was noted in the background (Liu stain, X200). Follow-up excision showed a secretory carcinoma (F, H&E, X200).

Figure 2. Oncocytic/squamoid subtype with benign follow-up. (A) Squamoid cell clusters noted in a background of mucoid material and granular debris (Papanicolaou, X200). (B) Follow-up excision showed a Warthin's tumor with focal mucinous and squamous metaplasia (H&E, X200). (C) Large, thickened cell fragments consisted of monotonous oncocytic/squamoid cells. The background was relatively clean (Papanicolaou, X200). (D) Follow-up excision showed an oncocytoma (H&E, X200).

Figure 3. Basaloid subtype. (A) Basaloid cell fragments showed membranous

extracellular matrix. The cells were devoid of atypia (Liu stain, X400). (B) Follow-up excision showed an adenoid cystic carcinoma with predominant tubular growth pattern (H&E, X200). (C) A cribriform cell cluster featured magenta-colored hyaline globules (Liu stain, X400). (D) Follow-up excision showed a basal cell adenoma with multiple microcysts containing basophilic substance. The tumor was well circumscribed with a thick fibrous capsule (H&E, X40).

Figure 4. Myoepithelial subtype. (A) Focal atypical cells with anisonucleosis and prominent nucleoli in a background of scant fibrillary stroma were noted, while the rest of the smear demonstrated classic features of a benign pleomorphic adenoma (Liu stain, X400). (B) The following parotidectomy specimen was totally embedded for sections and showed a benign pleomorphic adenoma with focal atypia (H&E, X200). (C) A cellular smear showed discohesive, plasmacytoid myoepithelial cells. Diffuse, mild to moderate atypia with anisonucleosis, binucleation, and distinct nucleoli were noted. There was no extracellular matrix identified on the smear (Liu stain, X400). (D) Follow-up excision showed a cellular pleomorphic adenoma (H&E, X200).